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Towards a Catalytic Atroposelective Synthesis of Diaryl Ethers via C(sp^2)-H Alkylation Using Nitroalkanes

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Abstract

Herein we report studies towards a small molecule catalytic approach to access atropisomeric diaryl ethers that proceeds via a C(sp^2)-H alkylation using nitroalkanes as the alkyl source. A quaternary ammonium salt derived from quinine containing a sterically hindered urea at the C-9 position was found to effect atroposelective C(sp^2)-H alkylation with moderate to good enantioselectivities across several naphthoquinone-containing diaryl ethers. Products can then be isolated in greater than 95:5 er after one round of trituration. For several substrates that were evaluated we observed a ‘nitroethylated’ product in similar yields and selectivities.

Graphical Abstract

Keywords

Atropisomerism; alkylation; phase-transfer catalysis; asymmetric catalysis; chirality

Atropisomerism is a type of chirality that occurs when there is hindered rotation about a bond, typically between two sp^2 atoms, wherein the rotational isomers are enantiomeric.^{1–5} While molecules that don’t possess adequate barriers to rotation aren’t considered atropisomeric,⁶ they possess the potential to be atropisomeric when engaging a chiral receptor (*i.e.* protein binding or interacting with a chiral catalyst).^{7–12}

Previous work from our group and others have demonstrated that atropisomer confirmation can be leveraged to improve various properties of biologically active small molecules.^{13–16} This work in part serves as call to action for the development of new synthetic methods

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Supporting Information

YES (this text will be updated with links prior to publication)

towards atropisomeric compounds. While there have been several excellent examples of atroposelective catalysis over the past few decades,^{17–20} the vast majority of examples have been on biaryl scaffolds. Examples of atroposelective catalysis on non-biaryl atropisomers have largely focused on benzamides and anilides.^{2,8,9}

Diaryl ethers are a type of atropisomer that have been largely overlooked by the enantioselective catalysis community despite their prevalence in natural products, exemplified by the macrocyclic diaryl ethers in vancomycin. Furthermore, atropisomerically unstable diaryl ethers are common motifs in drug discovery (Figure 1). Thus far, the literature involving diaryl ethers is highlighted by some nice diastereoselective examples en route to vancomycin²¹ and several excellent studies by Clayden and coworkers^{22–26} wherein they characterized the stereochemical stabilities of differently substituted diaryl ethers, and developed diastereoselective routes to atropisomeric diaryl ethers. Notably, in collaboration with Turner, they disclosed the only catalytic atroposelective route towards diaryl ethers currently in the literature, employing oxidase or reductase enzymes to desymmetrize prochiral diaryl ethers (Scheme 1A).

Other than these groundbreaking examples, work on the catalytic atroposelective synthesis of diaryl ethers has been scarce. Perhaps the major reason for this is that diaryl ethers possess two axes (Figure 1) that can complicate reaction development, analysis and in some cases, result in racemization at a lower-than-expected energy via a concerted gearing mechanism.^{23,27} When defining the chirality of diaryl ethers, Clayden and others have made an analogy to atropisomeric biaryl systems, defining chirality based on the orientation of the substituents across both aryl planes when looking down one aryl-ether axis (see Figure 1, priority assigned in example according to R group's number).

Recent work from our group has focused on the atroposelective synthesis of naphthoquinone-based biaryls via the rigidification of a rapidly interconverting axis via a 1,4-nucleophilic addition into the quinone.²⁸ As there is a lack of enantioselective routes towards atropisomeric diaryl ethers, we decided to test whether this approach could be extended to this scaffold (Scheme 1B). We chose to evaluate naphthoquinones such as **1a** where the aryl groups possessed a large *tert*-butyl group and a 2nd smaller substituent *ortho*-to the ether axis, as Clayden has shown that having one large quaternary substituent is often a prerequisite to obtain stereochemically stable diaryl ethers.

While evaluating nucleophiles for the addition into **1a**, we observed that the use of nitromethane in the presence of excess Cs₂CO₃ and tetrabutylammonium bromide (TBAB) resulted in the isolation of a C(*sp*²)-H methylated product **2a** (Table 1, entry 1), in line with seminal work reported by Mukherjee.^{29,30} Quinine derived quaternary amines with hydroxyl substitution at the cinchona alkaloid *C*-9 position gave nearly no observable selectivities (see SI for details). On the other hand, catalyst **C1**, which has a *C*-9 stereochemically inverted Boc-protected amine (Table 1, entry 2), yielded preliminary levels of enantioselectivity, albeit with low conversions to **2a**. The selectivity could be further improved to an enantiomeric ratio (er) of 85:15 when *tert*-butyl urea-containing catalyst **C2** was used.

The addition of water, or the use of other carbonate bases, resulted in a loss in selectivity with minimal increase in yield (Table 1, entries 4–6), however the use of tribasic potassium phosphate (Table 1, entry 7) resulted in an increase in yield to 60% with only a slight drop in selectivity (er of 80:20) when compared to Cs_2CO_3 . Finally, in line with Mukherjee's work, we found that the addition of 3 Å molecular sieves resulted in yields of **2a** approaching 70% with a small increase in selectivity to 81:19 er (Table 1, entry 10). While these selectivities may be considered moderate, **1a** can be further enantioenriched via trituration out of isopropanol to allow access of **2a** in greater than 97:3 er. **2a** proved to be moderately stable, with an experimentally determined barrier to rotation at 65°C of 26.6 kcal/mol, likely resulting in what LaPlante calls a "Type-II atropisomer" that would be expected to display significant racemization at room temperature over the course of a few weeks.

Extensive experimentation failed to yield further increases in er. Nonetheless, we decided to evaluate the conditions in Table 1, entry 10 across several differentially substituted substrate analogs (Figure 2).^{31–33} Substrate **1b**, where the aryl group possesses a 6-methyl substitution, resulted in a decrease in yield and enantioselectivity in the isolated product **2b** to 54% yield with an er of 71:29. Substrate **1c**, which possesses a 4-phenyl and 6-methyl substitution yielded **2c** with similar selectivities. These results could be explained by an increase in electron density on the ether, reducing the electrophilicity of the quinone. Diaryl ether **1d**, which possesses an electron deficient *para*-aryl ring, reinforces this hypothesis as the reaction proceeded with a large increase in yield of **2d** while retaining the moderate enantioselectivity (er of 71:29).

Substrate **1e**, which possesses 4-phenyl and 2-chloro substitution on the aryl ring also yielded moderate selectivities and yields of **2e** (47% yield, 72:28 er), however, we also observed small amounts of 'nitroethylated' **3e** (*vide infra*). Substrate **1f**, which possesses 6-Br substitution, yielded a 1:3 mixture of methylated **2f** (10%) and 'nitroethylated' **3f** (30%) yield. Interestingly, while **2f** was obtained in 78:22 er, **3f** was obtained in only 60:40 er. Surprisingly, one round of trituration with hexanes allowed for isolation of **3f** in 99:1 er, albeit in low overall yield. Substrate **1g**, which possesses 4,6-diphenyl substitution yielded exclusively 'nitroethylated' **3g** with a 75:25 er. We observed similar results with **1h** and **1i** which gave 'nitroethylated' **3h** and **3i** with similar yields and selectivities.

Referring back to Mukherjee's hypothesized mechanism of $\text{C}(\text{sp}^2)\text{-H}$ alkylation using nitroalkanes, we postulate that our diaryl ether substrates proceed via a quinone methide intermediate.²⁹ If this intermediate is long lived enough, then another equivalent of nitronate anion can add 1,4 into the quinone-methide to yield the 'nitroethylated' product (Scheme 2). While the exact mechanism of quinone-methide stabilization is unknown, we suspect it is due to a subtle electronic effect as 'nitroethylation' is only observed with substrates that possess electron neutral or donating substitution *para*- to the ether.

We next sought to define the stereochemical induction of this reaction. As we were unable to obtain suitable crystals, we compared experimental and computational circular dichroism (CD) spectra, a method that is gaining acceptance in the stereochemical community.^{34–36} We obtained CD spectra of highly enantioenriched (er>97:3) **2a** and compared it to computational CD spectra of **2a** of all possible stable conformations about both ether axes

(Scheme 3). This analysis suggests that the major product is in the S_a configuration with the proximal quinone carbonyl *endo*- to the aryl ring (S_a -*endo*).

As we generated these conformations for the computational CD studies we observed striking differences in their predicted energies (Scheme 3). For example, the S_a -*endo* conformation of **2a** is predicted to be significantly more stable than the S_a -*exo* conformation. Interestingly, we observed the opposite trend for the starting material **1a**, with the *exo*- conformation being more stable (see SI for more details).

To further investigate this, we generated contour energy maps of the rotational landscape about both axes (Scheme 3) of the diaryl ether. Consistent with results from Clayden,²³ these maps demonstrate that there is a low energy pathway for interconversion between the *exo*- and *endo*- conformations of a given enantiomer that proceeds via a concerted gearing mechanism. Thus, it is likely that the *exo*- conformation of the starting material is more stable and will likely be the conformation that interacts with the catalyst, however, the addition of the methyl group will lead to an immediate conformational gear shift to the *endo*- enantiomers.

Our working model for stereoiduction is shown in the proposed transition state in Scheme 2 in which we propose that the urea moiety of the catalyst to hydrogen bond with both the ether oxygen and one of the quinone carbonyls of the lower energy *exo*- diaryl ether conformation. From here, the diaryl ether is preorganized into the S_a -atropisomer to avoid steric interactions between the *tert*-butyl group and the quinuclidinium that would be present in the R_a atropisomer/catalyst complex. We postulate that the hydrogen bonding will activate the diaryl ether for nucleophilic attack by nitronate anion which will then undergo HNO₂ elimination followed by tautomerization to give alkylated quinone, or subsequent attack of nitronate followed by oxidation to give the 'nitroethylated' byproduct. At this point, it is likely that both products will rapidly relax to the *endo*- conformation, perhaps providing a release mechanism from the catalyst.

In conclusion we have disclosed to the best of our knowledge the first example of a small molecule catalytic synthesis of diaryl ethers. While our selectivities were moderate-to-good, highly enantioenriched ethers can be accessed via trituration. We also discussed several mechanistic aspects of this work. We hope that these studies will serve as a starting place for future efforts towards the enantioselective syntheses of diaryl ethers and related atropisomers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (31). General Procedure of Substituted Diaryl Ether Naphthoquinones To a scintillation vial, 10mg 3Å powdered M.S. was added with an oven dried stir bar. The sieves were activated and toluene was syringed into the vial (.1M). Diaryl ether naphthoquinone (.026mmol, 1 equiv), potassium phosphate tribasic (.26mmol, 10 equiv), quaternary ammonium salt Catalyst 2 (.0026mmol, .1 equiv) and nitromethane (.26mmol, 10 equiv) were added sequentially. The reaction was stirred at room temperature for 36 hours. The mixture was then diluted with toluene and filtered over Celite to remove excess base and molecular sieves. Purification with flash column chromatography (hexanes:DCM::100:0 to 80:20) afforded the desired methylated and nitroethylated products. (~3% to 68% yield).
- (32). Characterization of Methylated Diaryl Ether Naphthoquinone 2a ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dd, J = 7.7, 1.3 Hz, 1H), 7.91 (dd, J = 7.5, 1.5 Hz, 1H), 7.72 (td, J = 7.5, 1.5 Hz, 1H), 7.66 (td, J = 7.5, 1.5 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 2.26 (s, 3H), 1.38 (s, 9H). ¹³C NMR (101 MHz, CDCl₃): δ 185.01, 178.23, 154.23, 150.33, 142.76, 134.01, 133.37, 131.95, 130.49, 129.17, 128.39, 127.62, 126.47, 126.40, 126.29, 125.23, 35.85, 29.99, 9.73. MS (APCI): Calculated for C₂₁H₁₈Cl₂O₃ [M+H]⁺ = 390.3. Found 390.3 m/z.
- (33). Characterization of Nitroethylated Diaryl Ether Naphthoquinone 3f ¹H NMR (500 MHz, CDCl₃) δ 8.13 (dd, J = 7.6, 1.3 Hz, 1H), 7.93 (dd, J = 7.7, 1.3 Hz, 1H), 7.75 (td, J = 7.6, 1.4 Hz, 1H), 7.68 (td, J = 7.5, 1.4 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 4.80 – 4.68 (m, 2H), 3.59 (ddd, J = 13.2, 9.0, 6.9 Hz, 1H), 3.43 (ddd, J = 13.2, 8.8, 6.0 Hz, 1H), 2.35 (s, 3H), 1.37 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 184.16, 177.98, 155.80, 149.75, 135.52, 134.29, 133.68, 131.66, 130.66, 128.41, 127.85, 127.48, 126.70, 126.41, 124.44, 71.98, 35.54, 30.32, 29.70, 22.44, 20.94. Calculated for C₂₃H₂₂BrNO₅ [M+H]⁺ = 473.3. Found 473.3 m/z.
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Figure 1:
Illustrative examples of diaryl ethers

Figure 2:

[a] Reactions were performed on a 0.028 mmol scale with 10 equiv of both base and nitromethane in 0.1M PhMe. [b] The formation of both products was observed for substrates **a-i**. The major product is shown above with its respective yield and er. More information about product ratios can be found in the Supporting Information. [c] er was determined via HPLC through an average from at least two trials. [d] **2a** was triturated with HPLC grade isopropanol. [e] A mixture of both methylated and 'nitroethylated' product was detected via mass spectroscopy; only the methylated product **2e** was isolated and characterized. [f] **3f** was triturated with HPLC grade hexanes. See SI for more details.

Scheme 1:

A) Previous catalytic atroposelective route towards diaryl ethers. B) Proposed enantioselective alkylation of diaryl ethers.

Scheme 2:

Proposed mechanism for nucleophilic methylation. The key intermediate involves a quinone-methide which is influenced heavily by electronic effects off of the aryl ring. Stabilization of the intermediate can induce subsequent addition of nitromethane, forming the 'nitroethylated' product. We hypothesize that the urea catalyst interacts with both the diaryl ether and carbonyl oxygen of the substrate, thereby locking it into the *(S_a)-exo*-confirmation. Subsequent tautomerization or 2^{nd} addition of nitronate followed by oxidation provide diaryl ether products **2a** and **3a**, respectively.

Scheme 3:

A dihedral angle contour diagram, generated through a force field molecular model, conveys an energetically favorable pathway towards racemization through a concerted gearing mechanism (See the SI for more details). Substrate-catalyst interaction can induce the high energy *exo* confirmation, followed by immediate “gearing” to the respective *endo*-enantiomer.

Table 1:

Optimization of C(sp²)-H Methylation **1a**

Entry	Solvent	Catalyst	Base	Sieves	Yield (%)	er ^[b]
1	PhMe	TBAB	Cs ₂ CO ₃	-	18	---
2	PhMe	C1	Cs ₂ CO ₃	-	18	62:38
3	PhMe	C2	Cs ₂ CO ₃	-	17	85:15
4	PhMe/H ₂ O	C2	Cs ₂ CO ₃	-	40	50:50
5	PhMe	C2	Na ₂ CO ₃	-	20	60:40
6	PhMe	C2	K ₂ CO ₃	-	15	65:35
7	PhMe	C2	K ₃ PO ₄	-	60	80:20
8	PhMe	C2	K ₃ PO ₄	4Å	51	75:25
9	PhMe	C1	K ₃ PO ₄	4Å	36	64:36

Entry	Solvent	Catalyst	Base	Sieves	Yield (%)	er ^[b]
10	PhMe	C2	K ₃ PO ₄	3 Å	68	81:19
11	CH ₂ Cl ₂	C2	K ₃ PO ₄	3 Å	38	68:32
12	MTBE	C2	K ₃ PO ₄	3 Å	71	73:27

^[a] Reactions were performed on a 0.028 mmol scale with 10 equiv of both base and nitromethane in 0.1M solvent.

^[b] er was calculated by HPLC and results are reported as an average from at least two trials. See the Supporting Information (SI) for more details.